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COOPERATIVE STUDIES

Modifiers of Timing and Possible Triggers of Acute Myocardial Infarction in the Thrombolysis in Myocardial Infarction Phase II (TIMI II) Study Group

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Objectives. The aim of this study was to provide insight into the mechanism of acute myocardial infarction by determining the modifiers of timing and possible triggers of onset of infarction.

Background. A higher frequency of onset of acute myocardial infarction has been reported in the morning with a peak in the 1st 3 h after awakening. This observation suggests that the onset of infarction may be triggered by activity in the morning and at other times of the day.

Methods. The clinical history of the 3,339 patients entered into the Thrombolysis in Myocardial Infarction phase II study was analyzed to determine characteristics predicting a higher frequency of infarction between 6 AM and noon, and onset of infarction during exertion.

Results. A higher proportion (34.4%) of infarctions began in the morning (6 AM to noon) compared with other times of the day. Characteristics independently predicting a higher frequency between 6 AM to noon were no beta-adrenergic blocking agent use in the 24 h before infarction, no discomfort other than the index pain in the preceding 48 h, occurrence of the infarction on a weekday and no history of current smoking.

In 18.7% of patients, infarction occurred during moderate or marked physical activity. Independent predictors of exertion-related infarction included male gender, no history of current smoking, white race, no use of calcium channel blocking agents or nitrates in the preceding 24 h, the absence of either chest pain at rest in the 3 weeks before infarction or any pain in the preceding 48 h, the absence of new onset angina and the presence of exertional pain in the preceding 3 weeks. Compared with patients whose infarction occurred at rest or during mild activity, those with exertion-related infarction had fewer coronary vessels with ≥60% stenosis ($p = 0.002$) and were more likely to have an occluded infarct-related vessel after thrombolytic therapy ($p = 0.01$).

Conclusions. Further study of the timing and activity at onset of infarction may provide insight into the pathophysiologic mechanisms causing acute myocardial infarction and provide clues to preventive measures.

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A higher frequency of onset of acute myocardial infarction in the morning with a peak in the 1st 3 h after awakening has been reported (2–6). This observation suggests that the onset of infarction may be triggered by morning activity, perhaps mediated by increases in systemic arterial pressure, heart rate, adrenergic activity, vascular tone and platelet aggregability at a time when fibrinolytic activity is low (7). Insight into the importance of each of these processes has been obtained by analysis of differences in the timing of the onset of infarction among patients with specific characteristics. For example, the finding (2,8) that preinfarction use of beta-adrenergic blocking agents or aspirin reduces the morning peak of infarction suggests that the peaking in adrenergic activity and platelet reactivity contributes to the morning onset of infarction (7). Patients with prior congestive heart failure have been reported to have a prominent peak of onset of infarction in the evening (4), whereas those with non-Q wave infarction have a less pronounced circadian pattern (9).

Although the occurrence of myocardial infarction is more frequent between 6 AM and noon, the majority of events are not confined to this 6-h period. Because many of the physiologic changes described in the morning are produced by stressors such as physical activity (7), further evaluation of the role of physical stress immediately before infarction may provide clues to the mechanisms of the onset of myocardial infarction and its prevention.

Apart from the study of Hjalmarson and colleagues (4), previous studies of the timing of the onset of myocardial

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infarction have not used multivariate analyses to identify independent predictors of the higher morning frequency of infarction. Such analyses are important because associations are likely between characteristics such as pain before infarction and the use of anti-ischemic medication. Other limitations of prior studies include the absence of data on the relations among angiographic characteristics, mortality and the timing and level of activity at the onset of infarction.

The purpose of the present analysis was to utilize data obtained in the Thrombolysis in Myocardial Infarction phase II study (TIMI II) to examine the circadian pattern and level of physical activity at the onset of infarction. The TIMI II data base provides a large, well characterized patient group in whom multivariate analyses can be performed to identify independent determinants of timing and level of activity at the onset of infarction.

Methods

Study patients. The detailed methods of the TIMI II trial have been published elsewhere (1). The study group in this report consists of the 3,339 patients enrolled in TIMI II.

Inclusion criteria were chest discomfort suggestive of myocardial ischemia lasting ≥30 min, ST segment elevation ≥0.1 mV in two contiguous electrical leads, patient age <76 years and the feasibility of initiating tissue-type plasminogen activator (rt-PA) therapy within 4 h of the onset of pain. Exclusion criteria have been detailed previously (1). Informed consent was obtained from all patients who participated in the study. The protocol was approved by the institutional committee on human research at each of the 24 participating hospitals. After treatment with rt-PA and intravenous heparin, patients were randomly assigned either to an invasive strategy, in which all patients underwent cardiac catheterization, or to a conservative strategy, in which catheterization was performed only for clinical indications.

Study protocol and definitions. The time of onset of symptoms of myocardial infarction and the level of physical activity at the onset of symptoms were recorded for each patient. To examine the effect of characteristics on timing, the day was divided into four 6-h periods. The 6 AM to noon period was subsequently compared with the remaining periods. The activity level at the onset of symptoms was classified as sleep, rest or mild, moderate or marked activity. Examples of each level of activity were provided to the nurse coordinator; rest was defined as lying in bed or sitting, mild activity as walking, moderate activity as climbing stairs and marked activity as running. An infarction whose onset occurred during moderate or marked activity was defined as exertion-related infarction. Patients were classified as at low risk when none of the following characteristics were present at study entry: history of prior infarction, ST segment elevation in the anterior electrocardiographic (ECG) leads, pulmonary rales in ≥1/3 of the lung fields, systolic blood pressure <100 mm Hg and sinus tachycardia ≥100 beats/min, atrial fibrillation or flutter, age ≥70 years, pulmonary edema at study entry and cardiogenic shock. Coronary perfusion status was graded according to previously published TIMI criteria: grade 0 indicates no flow; grade 1, penetration without perfusion; grade 2, full perfusion with slow flow, and grade 3, full perfusion with normal flow.

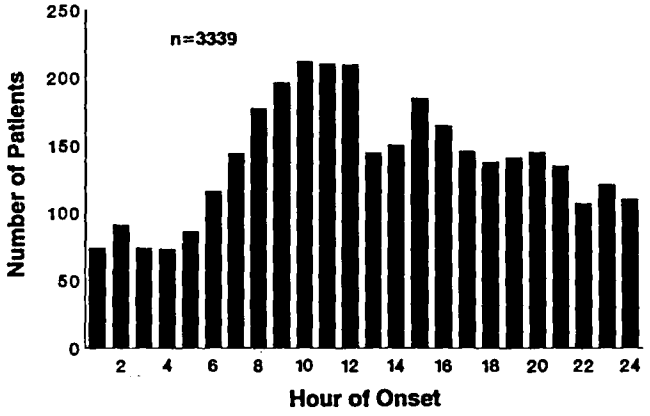

Figure 1. Hourly frequency of the onset of myocardial infarction as determined by the onset of pain symptoms in 3,339 patients.

Statistical analysis. The results presented in this report are based on all data received in the TIMI Coordinating Center as of January 1991. Baseline data are presented using percentages or mean values and standard deviations. An extensive list of clinical characteristics was investigated for possible associations with the outcomes of timing and level of physical activity at the onset of infarction as univariate modifiers. The relation among baseline characteristics and the timing and level of activity at onset were ascertained by using analysis of variance or a stepwise logistic regression model for multivariate analyses (10). A p value ≤ 0.01 was required for all variables remaining in the final model. Analyses were performed by using either a Biomedical Data Package (BMDP) (11) or Statistical Analysis System (SAS) programs (12). To adjust for the effects of multiple testing, p values of 0.01 to 0.001 were judged as providing some evidence of group differences, and p values < 0.001 were judged as providing strong evidence of group differences not due to chance alone.

Results

Timing of onset of myocardial infarction (Fig. 1 to 3, Tables 1 and 2). In the overall study group, there was a higher frequency of onset of myocardial infarction in the morning; 34.4% of infarctions occurred between 6 AM and noon whereas 15.4% occurred between midnight and 6 AM (Fig. 1). The association between baseline patient characteristics and infarction characteristics and the timing of the onset of infarction is described in Table 1. Stepwise logistic regression analysis (Table 2) revealed the following *independent* predictors of a higher frequency between 6 AM and noon compared with other times of the day: an absence of chest

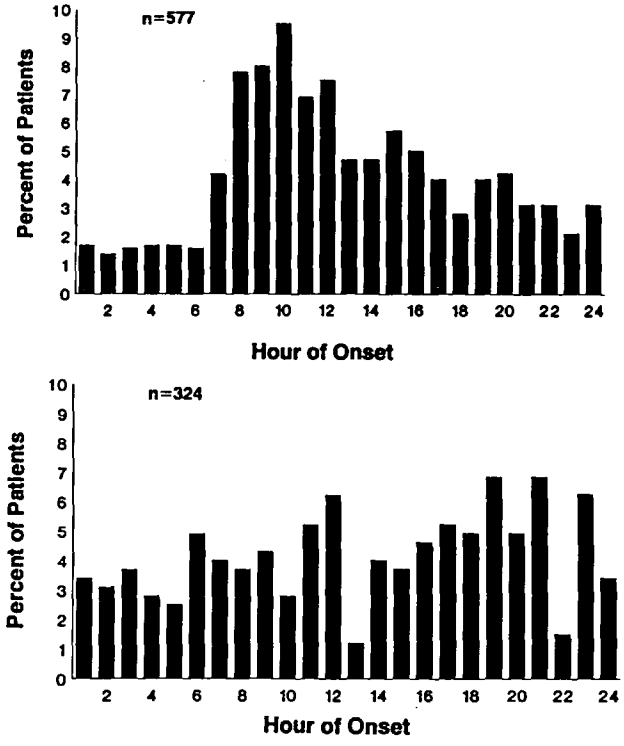

Figure 2. Hourly frequency of the onset of myocardial infarction based on the presence of characteristics found to independently predict an increased frequency between 6 AM and noon: no beta-blocker use in the 24 h before infarction, no pain other than the index pain in the preceding 48 h, occurrence of infarction on a weekday and current nonsmoking status. **Top**, 577 patients with all four predictors. **Bottom**, 324 patients with no or one predictor.

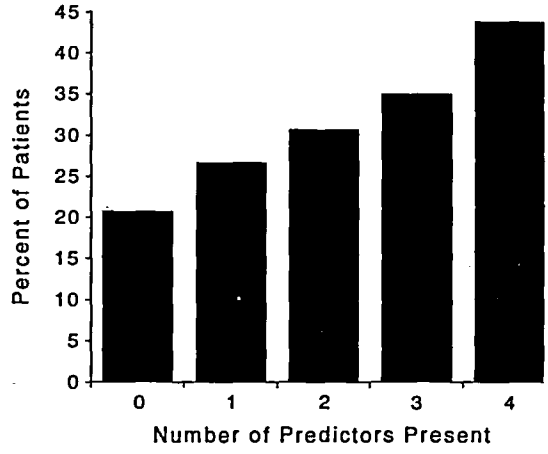

Figure 3. Percent of patients with the onset of myocardial infarction between 6 AM and noon. The likelihood of onset of infarction in this period increases with the number of predictors present: 20.8% (5 of 24) with no predictors present; 26.7% (80 of 300) with one predictor; 30.7% (311 of 1,014) with two predictors; 35.0% (499 of 1,424) with three predictors, and 43.8% (253 of 577) with all four predictors. The predictors are described in Figure 2.

pain within the preceding 48 h, absence of beta-blocker use within the 24 h before infarction, no history of current cigarette smoking and onset of infarction on a weekday. In Figure 2, the timing pattern is compared in patients with no or one predictor of morning infarction and in those with all four predictors. The relation between the number of predictors and the frequency of onset of infarction between 6 AM and noon is depicted in Figure 3.

In TIMI II, 1,681 patients (50%) were randomly assigned to protocol catheterization after thrombolytic therapy; catheterization was performed in 1,500 of these patients. In this large subset of patients, there was no association between the time of onset of infarction and infarct-related artery patency (TIMI flow grade) or the number of coronary vessels with stenoses ≥60%.

The 42-day mortality rate tended to be higher for patients with an onset of infarction between 6 AM and noon than in those with an onset at other times of day, but the number of deaths was relatively small and the power to detect a difference was limited. Reinfarction rates at 42 days did not differ among groups.

Physical activity at the onset of myocardial infarction (Tables 3 and 4). Myocardial infarction began during exertion in 18.7% of patients (during moderate activity in 12.9% and during marked activity in 5.8%) and during rest conditions in 81.2% (during sleep in 13.8%, at rest in 36.0% and during mild activity in 31.4%). Univariate predictors of exertion-associated infarction are listed in Table 3. Stepwise logistic regression analysis indicated that those patients most likely to have an infarction associated with exertion had no other chest pain in the preceding 48 h, were male, had exertional pain in the preceding 3 weeks, no pain at rest in the preceding 3 weeks, no nitrate use in the preceding 24 h, no new onset angina in the preceding 3 weeks, no calcium channel blocker use in the preceding 24 h, no history of hypertension, were white and had no history of current smoking (Table 4). The first four of the aforementioned variables were associated with an odds ratio ≥2.0 (that is, when the variable was present, the onset of infarction was at least twice as likely to occur during exertion as during rest). The relation between the likelihood of infarction beginning during exertion and the number of variables present with an odds ratio >2.0 is depicted in Figure 4.

Patients with exertion-associated infarction who were randomized to undergo routine coronary angiography after thrombolysis were more likely than those with rest-associated infarction to have no significant (≥60%) stenosis (16.8% vs. 9.2%, $p < 0.001$), although they were also more likely to have an infarct-related artery that was occluded (19.4% vs. 13.8%, $p = 0.01$). Both 42-day mortality and recurrent infarction rates tended to be lower in those with exertion-related infarction (3.0% vs. 5.3%, $p = 0.02$ and 4.2% vs. 7.2%, $p = 0.006$, respectively). Baseline plasma fibrinogen levels (13) were also significantly lower in patients with exertion-associated infarction than in those with infarction occurring at rest (294 ± 74 [n = 319] vs. 310 ± 86 mg/dl [n = 1,425], $p = 0.002$).

Table 1. Time of Onset of Myocardial Infarction (hour of day)

	Midnight to 6 AM		6 AM to Noon		Noon to 6 PM		6 PM to Midnight		
	n	(%)	n	(%)	n	(%)	n	(%)	p Value*
All patients	514	(15.4)	1,148	(34.4)	924	(27.7)	753	(22.6)	<0.001
Patient characteristics									
Age									
≥65 years	110	(12.8)	318	(37.0)	237	(27.6)	194	(22.6)	0.06
<65 years	404	(16.3)	830	(33.5)	687	(27.7)	559	(22.5)	
Gender									
Male	424	(15.5)	943	(34.4)	765	(27.9)	610	(22.2)	0.98
Female	90	(15.1)	205	(34.3)	159	(26.6)	143	(24.0)	
Race									
White	447	(15.2)	1,022	(34.7)	820	(27.8)	659	(22.4)	0.34
Nonwhite	67	(17.1)	126	(32.2)	104	(26.6)	94	(24.0)	
Diabetes mellitus									
Yes	62	(14.1)	155	(35.3)	101	(23.0)	121	(27.6)	0.66
No/unknown	452	(15.6)	933	(34.2)	823	(28.4)	632	(21.8)	
Current smoker									
Yes	267	(16.3)	522	(31.8)	452	(27.6)	399	(24.3)	0.002
No/unknown	247	(14.5)	626	(36.8)	472	(27.8)	354	(20.8)	
Prior infarction									
Definite/suspected	87	(18.6)	147	(31.4)	119	(25.4)	115	(24.6)	0.14
No/unknown	427	(14.9)	1,001	(34.9)	805	(28.0)	638	(22.2)	
Hypertension									
Yes	229	(17.9)	413	(32.3)	331	(25.9)	306	(23.9)	0.04
No/unknown	285	(13.8)	735	(35.7)	593	(28.8)	447	(21.7)	
History of CHF									
Yes	14	(15.2)	24	(26.1)	25	(27.2)	29	(31.5)	0.09
No/unknown	500	(15.4)	1,124	(34.6)	898	(27.7)	724	(22.3)	
No angina in prior 48 h									
Yes	240	(18.8)	399	(31.2)	332	(25.9)	309	(24.1)	0.002
No	274	(13.3)	749	(36.4)	592	(28.8)	444	(21.6)	
Low risk†									
Yes	156	(14.0)	384	(34.5)	322	(28.9)	251	(22.6)	0.92
No	358	(16.1)	764	(34.3)	602	(27.0)	502	(22.6)	
Day of onset									
Saturday or Sunday	148	(15.8)	286	(30.5)	281	(29.9)	224	(23.9)	0.003
Weekday	366	(15.2)	862	(35.9)	643	(26.8)	529	(22.0)	
Angina within prior 3 weeks									
None									
Yes	264	(13.6)	685	(35.2)	569	(29.2)	429	(22.0)	0.25
No	250	(18.0)	463	(33.3)	355	(25.5)	324	(23.3)	
At rest									
Yes	119	(19.1)	209	(33.5)	149	(23.9)	147	(23.6)	0.60
No	395	(14.6)	939	(34.6)	775	(28.6)	606	(22.3)	
Exertional									
Yes	125	(17.0)	263	(35.7)	189	(25.6)	160	(21.7)	0.40
No	389	(15.0)	885	(34.0)	735	(28.2)	593	(22.8)	
New onset									
Yes	103	(16.2)	216	(34.1)	162	(25.6)	153	(24.1)	0.85
No	411	(15.2)	932	(34.4)	762	(28.2)	600	(22.2)	
Increasing frequency									
Yes	89	(18.0)	164	(33.3)	132	(26.8)	108	(21.9)	0.57
No	425	(14.9)	984	(34.6)	792	(27.8)	645	(22.7)	
At night									
Yes	44	(24.4)	55	(30.6)	38	(21.1)	43	(23.9)	0.27
No	470	(14.9)	1,093	(34.6)	886	(28.0)	710	(22.5)	
Medication in prior 24 h									
Beta-blockers									
Yes	109	(18.5)	174	(29.5)	151	(25.6)	155	(26.3)	0.006
No	405	(14.7)	974	(35.4)	773	(28.1)	598	(21.8)	
Nitrates									
Yes	130	(17.9)	230	(31.6)	193	(26.6)	174	(23.9)	0.08
No	384	(14.7)	918	(35.2)	731	(28.0)	579	(22.2)	
Calcium channel blockers									
Yes	92	(19.9)	142	(30.7)	115	(24.9)	113	(24.5)	0.08
No	422	(14.7)	1,006	(35.0)	809	(28.1)	640	(22.2)	
Aspirin									
Yes	67	(18.6)	117	(32.4)	98	(27.2)	79	(21.9)	0.40
No	447	(15.0)	1,031	(34.6)	826	(27.7)	674	(22.6)	
Angiographic characteristics‡									
Flow in infarct-related artery									
TIMI grade 2,3 (open)	199	(15.6)	434	(34.1)	387	(30.4)	252	(19.8)	0.50
TIMI grade 0,1 (closed)	29	(12.9)	82	(36.4)	60	(26.7)	54	(24.0)	
Vessels with ≥60% stenosis									
0	19	(12.2)	58	(37.2)	54	(34.6)	25	(16.0)	0.88
1	119	(14.5)	288	(35.1)	244	(29.8)	169	(20.6)	
2	65	(17.9)	124	(34.1)	100	(27.5)	75	(20.6)	
3	19	(17.4)	36	(33.0)	29	(26.6)	25	(22.9)	
42-day event rate									
Recurrent infarction	31	(6.0)	75	(6.5)	71	(7.7)	45	(6.0)	0.85
Mortality	22	(4.3)	70	(6.1)	36	(3.9)	37	(4.9)	0.03

*p values based on comparison of 6 AM to noon versus average of other time points. †See Methods section for definition of low risk. ‡Patients in invasive strategy. CHF = congestive heart failure; TIMI = Thrombolysis in Myocardial Infarction.

Table 2. Factors Correlated With Higher Frequency of Myocardial Infarction Between 6 AM and Noon

	Odds Ratio*	p Value	99% CI
No beta-blocker use in prior 24 h	1.34	<0.01	1.03–1.73
Not a current smoker	1.30	<0.01	1.07–1.57
Onset during weekday	1.28	<0.01	1.03–1.58
No angina in prior 48 h	1.26	<0.01	1.04–1.54

*An odds ratio >1.0 for a variable indicates that onset of infarction is more likely to occur between 6 AM and noon when the variable is present. CI = confidence interval.

Discussion

Timing of onset of infarction. The TIMI II patients had a morning peak in frequency of onset of myocardial infarction. The morning increase (6 AM to noon compared with midnight to 6 AM) was even more prominent in TIMI II (34.4% vs. 15.4%) than among patients enrolled in the Multicenter Investigation of the Limitation of Infarct Size (MILIS) based on time of symptom onset (2) (29.9% vs. 22.0%) (p = 0.001, Pearson chi-square). Differences in inclusion criteria between the two studies may account for the differences in timing of onset. The TIMI II study required ST segment elevation for enrollment, whereas the MILIS study enrolled patients with either ST segment depression or elevation. In a recent analysis of non-Q wave myocardial infarction by Kleiman and colleagues (9), no diurnal pattern was observed. As occlusive thrombosis is more likely to be associated with ST segment elevation than with ST segment depression, these data suggest that a relatively hypercoagulable state in the morning (7) may predispose to Q wave myocardial infarction at that time. The patient group with the highest frequency (43%) of infarction onset between 6 AM and noon in the present study comprised those patients who had no preinfarction angina or recent beta-blocker use, who were not currently smoking cigarettes and whose index event began on a weekday. In contrast, the group with the lowest frequency (21%) of infarction between 6 AM and noon had none of these characteristics.

Our finding that beta-blocker use within 24 h of the onset of infarction reduced the proportion of morning infarctions is consistent with results from previous studies (2–4) and supports the hypothesis that adrenergic activation contributes independently to the increased frequency of morning onset of infarction. The preinfarction use of calcium channel blockers and nitrates showed a nonsignificant trend (p = 0.08) to reduce the proportion of morning infarctions, possibly by reducing the increased morning vascular tone (14). In the present study, prior use of aspirin did not significantly alter the timing of onset of infarction. By contrast, use of aspirin markedly reduced the proportion of morning events in the Physician's Health Study (8). The observed difference may have resulted from the fact that the latter study was a

Table 3. Level of Physical Activity at Symptom Onset

	Sleep/Rest/Mild		Moderate/Marked		
	n	(%)	n	(%)	p Value*
All patients	2,712	(81.3)	625	(18.7)	
Patient characteristics					
Age					
≥65 years	726	(84.7)	131	(15.3)	0.003
<65 years	1,986	(80.1)	494	(19.9)	
Gender					
Male	2,172	(79.2)	570	(20.8)	<0.001
Female	540	(90.8)	55	(9.2)	
Race					
White	2,376	(80.6)	570	(19.4)	0.01
Nonwhite	336	(85.9)	55	(14.1)	
Diabetes mellitus					
Yes	374	(85.2)	65	(14.8)	0.02
No	2,338	(80.7)	560	(19.3)	
Current smoker					
Yes	1,343	(81.9)	297	(18.1)	0.37
No/unknown	1,369	(80.7)	328	(19.3)	
Prior infarction					
Definite/suspected	417	(89.1)	51	(10.9)	<0.001
No/unknown	2,295	(80.0)	574	(20.0)	
Hypertension					
Yes	1,102	(86.2)	177	(13.8)	<0.001
No/unknown	1,610	(78.2)	448	(21.8)	
History of CHF					
Yes	81	(88.0)	11	(12.0)	0.09
No	2,630	(81.1)	614	(18.9)	
No angina in prior 48 h					
Yes	1,564	(76.0)	495	(24.0)	<0.001
No	1,148	(89.8)	130	(10.2)	
Low risk†					
Yes	870	(78.2)	243	(21.8)	0.001
No	1,842	(82.8)	382	(17.2)	
Day of onset					
Saturday or Sunday	759	(81.0)	178	(19.0)	0.80
Weekday	1,953	(81.4)	447	(18.6)	
Angina within prior 3 weeks					
None					
Yes	1,501	(77.1)	446	(22.9)	<0.001
No	1,211	(87.1)	179	(12.9)	
At rest					
Yes	576	(92.3)	48	(7.7)	<0.001
No	2,136	(78.7)	577	(21.3)	
Exertional					
Yes	607	(82.4)	130	(17.6)	0.39
No	2,105	(81.0)	495	(19.0)	
New onset					
Yes	565	(89.1)	69	(10.9)	<0.001
No	2,147	(79.4)	556	(20.6)	
Increasing frequency					
Yes	442	(89.7)	51	(10.3)	<0.001
No	2,270	(79.8)	574	(20.2)	
At night					
Yes	166	(92.2)	14	(7.8)	<0.001
No	2,546	(80.6)	611	(19.4)	
Medication in prior 24 h					
Beta-blockers					
Yes	522	(88.6)	67	(11.4)	<0.001
No	2,190	(79.7)	558	(20.3)	
Nitrates					
Yes	660	(90.9)	66	(9.1)	<0.001
No	2,052	(78.6)	559	(21.4)	
Calcium channel blockers					
Yes	423	(91.6)	39	(8.4)	<0.001
No	2,289	(79.6)	586	(20.4)	
Aspirin					
Yes	300	(83.1)	61	(16.9)	0.34
No	2,412	(81.0)	564	(19.0)	
Angiographic characteristics‡					
Flow in infarct-related artery					
TIMI grade 2,3 (open)	1,032	(81.1)	240	(18.9)	0.01
TIMI grade 0,1 (closed)	166	(73.8)	59	(26.2)	
Vessels with ≥60% stenosis					
0	107	(68.6)	49	(31.4)	0.002
1	660	(80.5)	160	(19.5)	
2	300	(82.4)	64	(17.6)	
3	91	(83.5)	18	(16.5)	
42-day event rate					
Recurrent infarction	196	(7.2)	26	(4.2)	0.006
Mortality	144	(5.3)	19	(3.0)	0.02

*p values based on comparison of 6 AM to noon versus average of other time points. †See Methods section for definition of low risk. ‡Patients in invasive strategy. Abbreviations as in Table 1.

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Table 4. Factors Correlated With Higher Frequency of Myocardial Infarction During Exertion

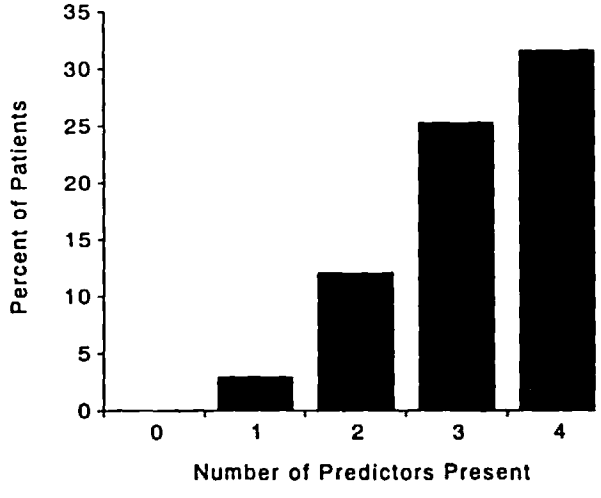
	Odds Ratio*	p Value	99% CI
No angina in prior 48 h	2.46	<0.001	1.80–3.36
Male	2.20	<0.001	1.48–3.27
Exertional angina in prior 3 wk	2.14	<0.001	1.52–3.02
No angina at rest in prior 3 wk	2.01	<0.001	1.28–3.12
No nitrates in prior 24 h	1.94	<0.001	1.31–2.89
No new onset angina in prior 3 wk	1.63	<0.001	1.10–2.42
No calcium channel blocker in prior 24 h	1.62	0.01	0.98–2.68
No hypertension	1.56	<0.001	1.20–2.03
White	1.47	0.01	0.98–2.21
Not a current smoker	1.28	0.01	1.00–1.63

*An odds ratio >1.0 indicates that when the factor is present, the onset of infarction is more likely to occur during exertion than during rest. CI = confidence interval.

randomized, prospective evaluation of aspirin with a greater power to detect an effect.

The frequency of morning infarction was also significantly greater during weekdays than on the weekend. This difference, which was also reported in MILIS (2), may result from the physical and mental stresses associated with the work week. Alternatively, this finding may be due to the later time that persons awaken and begin physical or mental activity on the weekend and the lesser intensities of these two activities.

Figure 4. Percent of patients with the onset of myocardial infarction during exertion. The relation between the likelihood of infarction beginning during exertion and the number of predictors present with odds ratio >2.0 (that is, when the variable was present, onset was more than twice as likely to occur during exertion as during rest): 0% (0 of 64) with no predictors present, 3% (10 of 328) with one predictor, 12.1% (127 of 1,051) with two predictors, 25.3% (444 of 1,755) with three predictors and 31.6% (44 of 139) with all four predictors. The predictors were male gender, absence of other chest pain in the preceding 48 h, absence of any rest pain in the preceding 3 weeks and exertional angina in the preceding 3 weeks.



Patients with the onset of infarction between 6 AM and noon were more likely to have had no other angina during the 48 h before onset. Although this observation may result from pathophysiologic differences between patients with or without prior angina, it may also be due to a reduction in level of morning activity in patients with preinfarction angina.

Although a relatively prothrombotic state is present in the morning, owing in part to elevated levels of plasminogen activator inhibitor and platelet aggregability (7), the time of onset of myocardial infarction did not alter response to rt-PA, as assessed by TIMI grade flow in the infarct-related vessel after therapy. An early difference in reperfusion rate response to rt-PA (15,16) cannot be excluded because cardiac catheterization in TIMI II was usually performed 18 to 48 h after the onset of infarction. Kurnik (16) recently reported that angiographic coronary artery patency 90 min after administration of rt-PA was lower in patients treated between midnight and noon than in those treated between noon and midnight (65% vs. 72%, $p < 0.05$).

Physical activity. The presence of a morning peak in the onset of infarction suggests that the onset is not a random event but may be triggered by external factors. Because several physiologic factors that increase in the morning, such as arterial pressure, heart rate, plasma catecholamine concentration and sympathetic nervous system activity, also increase with physical activity, it has been proposed that physical activity at any time during the day may trigger acute infarction (7,17). The findings in the present study, in which myocardial infarction occurred during moderate or marked activity in 18.7% of patients, are consistent with this hypothesis, because moderate or marked activity would have constituted a proportionately much smaller fraction of the 24-h day. Patients with a high frequency (31.6%) of infarction commencing during moderate or marked exertion were men with exertional but not rest angina in the preceding 3 weeks, and with no angina in the preceding 48 h.

Patients with exertion-associated infarction were more likely than those with rest-associated events to have no vessel with significant stenosis after thrombolytic therapy. This finding suggests that physical exertion may trigger plaque rupture and occlusive thrombosis in the absence of severe atherosclerotic narrowing. Conversely, patients with exertion-related infarction were more likely than those with rest-related infarction to have an occluded infarct-related vessel at the time of coronary arteriography. This finding may be due to a more severe plaque rupture in these patients, exposing a more thrombogenic surface and resulting in increased platelet deposition and an occlusion less susceptible to lysis. These patients tended to have lower rates of recurrent infarction and mortality. The lower event rate among those with exertion-associated infarction may result from a lower long-term risk profile in these patients

and from a lower reocclusion rate of initially patent arteries after thrombolysis.

Patients with preinfarction angina were also less likely than those without prior angina to experience the onset of infarction during physical activity. It is possible that these patients had a decreased likelihood of experiencing the index event during physical activity simply because they spent a smaller part of the day engaged in such activity. A similarly reduced time spent on physical activity may explain why patients receiving calcium channel blockers, nitrates or beta-blockers were less likely to experience the onset of infarction during activity. Nevertheless, there is a recurrent association that those patients with the most coronary artery disease risk factors and poorest baseline characteristics were the most likely to have infarction at rest or during mild activity. This observation suggests that patients with more severe coronary artery disease may have more fragile or vulnerable plaques that are prone to rupture readily whereas patients with fewer risk factors have fewer vulnerable plaques that require a more strenuous external stress (moderate to marked activity) to precipitate rupture. A better assessment of the role of physical activity as a trigger of infarction requires an adjustment such as that proposed by Maclure (18) to account for the usual portion of time spent in the activity (19). No data of this type were collected in TIMI II.

Physical activity and plaque rupture. Evidence supports a link between physical exertion and rupture of a coronary artery plaque. In a rabbit model, a combination of a pressor surge induced by epinephrine and a hypercoagulable stimulus from Russell viper venom resulted in plaque rupture and thrombosis (20). Using autopsy specimens and computer-simulated stress-strain relations, investigators (21,22) have suggested that an acute increase in arterial pressure or heart rate, such as that associated with physical exertion, may predispose to rupture. Ideally, understanding of the pathophysiology of the onset of infarction would require knowledge of the state of hemodynamics (arterial pressure and heart rate), hemostasis and vasoreactive forces in the minutes before plaque rupture and occlusive thrombus formation. The absence of these data (which are inherently unobtainable for the majority of patients with infarction) limits testing of the triggering hypothesis. However, because the changes in these processes produced by exertion and other potential triggering activities are known, it is possible to gain insight into the processes causing infarction by studying the activities before its onset.

Conclusions. Further study of the timing of the onset of infarction, together with a study of specific plaque characteristics in different patient subgroups, may provide further insight into the pathophysiologic mechanisms of the onset of infarction. Similarly, determination of the role of possible triggers of infarction, such as physical activity, may provide new strategies for prevention.

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